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13. ABSTRACT (Maximum 200 words)

Our training program in the detection and treatment of breast cancer has provided an excellent training opportunity to those interested in pursuing research careers in this interdisciplinary area. We have structured our program so that each of the four predoctoral trainees were assigned dual advisors. Each trainee was supervised by a well trained basic scientist as well as a clinician. In addition, each trainee attended weekly journal club meetings and monthly seminars. The field of research encompasses a wide variety of disciplines including Genetics, Biophysics, Biochemistry, Physiology, Tumor Biology, Electrical Engineering, and Computer Science as well as many clinical fields (including Surgery, Radiology, Oncology, Radiation Therapy).

The University of Pennsylvania has developed a unique broadly based interdisciplinary program of graduate education aimed at applying physical principles to the clinical problems inherent in the detection and treatment of breast cancer. During the past year our main research effort was aimed at improving the detection and treatment of breast cancer. This effort involved many aspects of detection both by imaging breast cancers as well as genetic screening. We began the development of improved treatment protocols based on increased knowledge of the metabolism of breast disease.

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J S Leigh 28 Aug 95

PI - Signature Date

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INTRODUCTION

The training program in Breast Cancer Detection and Treatment has provided important training opportunities to the four predoctoral fellows funded by this grant. Their research encompassed a wide variety of disciplines including Genetics, Biophysics, Biochemistry, Physiology, Tumor Biology, Electrical Engineering, and Computer Science as well as many clinical fields including Surgery, Radiology, Oncology, and Radiation Therapy. Our program established many working relationships in the technical developments and clinical problems involved in breast cancer.

Our main goal was aimed at improving the detection and treatment of breast cancer. These efforts have involved many aspects of detection both by imaging breast cancers as well as genetic screening. We have concentrated our efforts both on the improvements of the hardware required to form magnetic resonance images and on the theory of the data acquistion process itself.

BODY

We used the following methods to improve the detection and treatment of breast cancer:

1.) Our studies on magnetic resonance hardware used for high resolution breast imaging included computer modelling, prototype construction, and engineering of the final forms of both novel radiofrequency multi-coil arrays and a new design for high resolution biplanar imaging gradients. Both of these new designs improved the sensitivity and capability of the breast imaging project. The radiofrequency coil improved the overall sensitivity of the imaging process by 30%, allowing higher signal-to-noise ratio images to be obtained at present resolution levels or alternately, higher resolution images to be obtained in the same period of time. The biplanar gradient design, which produced homogeneous gradients of roughly 6 gauss/cm over the breast, were designed and constructed to function with the new radiofrequency coil design in addition to allowing access to allow for the possibility of MR guided breast and localization of tumors which might otherwise be invisible to conventional mammography. Because the biplanar gradients were successfully interfaced to the clinical imaging system at the Hospital of the University of Pennsylvania with appropriate new eddy current compensation all of the standard clinical pulse sequences available could be interfaced with the enhanced capabilities of the biplanar gradients. The increased strength of the biplanar gradient design over the standard gradients available on the clincal magnetic resonance imager allows images with resolutions roughly 6 times higher than the standard images to be obtained. The smallest imaging field of view that could be obtained with the biplanar gradient set was roughly 2 centimeters.

2.) We used surface coils to study breast tissues, which are located outside the body cavity. Surface coils not only enhance breast tissue's signal to noise ratio, but also decrease the necessary amount of RF power deposition in the body during RF pulsing. In addition, surface coils can provide easy localization of the NMR signal to breast tissue in the absence gradients or other means of localization.

The localized sensitive volume of the surface coil also prevents the aliasing of signal from outside of breast into the field of view during imaging of breast or parts of the breast. However, the B1 fields generated by the surface coils are not uniform, which results in variations in tip angles throughout the sensitive volume. For

example, in spin echo imaging, this can cause severely distortions. One way to excite uniform tip angles across an imaging volume with surface coils is to use adiabatic pulses. We have been investigating the combination of adiabatic half passage and adiabatic refocusing pulses with surface coils in alleviating the distortions caused by the non-uniform B1 fields.

Computer simulations of the distribution of B1 amplitudes in the sensitive volume of the surface coil are done in combination with simulations of the motions of the magnetization vectors under the adiabatic pulses at these B1 values in order to predict the resultant tip angles within the sensitive volume of a surface coil after adiabatic pulses. The shapes of both of the adiabatic pulses are numerically optimized to broaden the range of B1 in which it can still achieve a fixed tip angle. Spin echo images of phantoms are obtained using the surface coil - adiabatic pulse combination.

The STEAM pulse sequence can be used in combination with surface coils to achieve precise spatial localization while preserving the signal to noise advantage. We have shown, via phantom experiments, that precise spatial localization can be acheived using the STEAM-surface coil combination. We have also designed simple methods of calibrating the 90 degree pulses at desired locations. These have also been demonstrated to work in phantom experiments.

3.) Theoretical studies of the magnetic resonance data acquistion process have also been ongoing with two specific goals in mind. First, increase the inherent sensitivity of the acquisition process by manipulation of the available parameters in the pulse sequence and data acquisition. Any process which increases the inherent sensitivity of the imaging process will allow images of better quality, higher resolution, and shorter imaging times to be acquired. Second, increase the resolution of the data gathered by novel manipulation of the digitization of the data that is acquired in the imaging process. Increasing the sensitivity of the imaging process requires foreknowledge of the relaxation parameters of the tissue of interest. Once both the transverse relaxation time is known, the theoretical resolution that can be obtained is known. Knowledge of the longitudinal relaxation time provides information regarding the optimal pulse power and repetition times. Although, individually, each of these parameters points to an optimal method of data acquisition in order to maximize either resolution or sensitivity they are not all necessarily independent of one another. Once the question is framed: "How do I get an image of the highest

possible resolution in the shortest period of time?" the optimal choice of pulse sequence, pulse power, repetition rate, data matrix, field-of-view, and data acquisition rate becomes a much more complicated, and clearly interdependent, optimization problem. A prescription has been formed which, when knowledge of the longitudinal and transverse relaxation times is available, will enable each of these parameters to be set in a novel optimal fashion. In addition, in order to enhance the resolution of the images obtained with the newly developed optimum prescription the digitization of the data has been altered to limit errors introduced by the limited bit resolution in the analog-to-digital converters (ADC). Since the data which reperesents the high resolution information in the image resides at the edges of the "k-space", where the peak signal levels are typically lower than at the center of k-space, the gain levels are not optimally set to accurately digitize this information. That is because the gain level for any given imaging sequence is typically set such that the highest signal level will just fill the ADC and thus be digitized to the limit of the hardware's capability. Thus, with the special capabilities of the home built spectrometer at our facility we can vary the gain level dynamically to a time resolution of 10 microseconds or better. Thus, we could vary the gain level between each acquisition point if desired. Simulations of the effects of this technique indicate that in lower level signal to noise ratio images the noise level may be significantly reduced because a large part of it is due to digitization noise. In images with higher levels of signal this effect is small. However, the regions of the image in which high fourier component information exists, mainly edges, the image quality is greatly enhanced allowing much better discrimination of edge features. Experiments applying this techniqued have been performed on biological phantoms with great success.

4.) In the imaging area, we performed Changeable Repetition Times and Weighted Data Window for Optimum Signal Acquisition in k-Space. In the center of the raw data space, the so-called k-space, the data points (low frequency data points) are characterized with better signal to noise ratio but with less information about the image resolution; while for data points far from the k-space center (high frequency data points), they contain more information about the image resolution but with deteriorated signal to noise ratio. For most purposes, people prefer to trade resolution for better signal to noise ratio, given limited imaging time acceptable for the subject in magnet. In this case, we can devise some method in software to save

imaging time while getting good quality image. The experiments we did proved that this is achievable.

5.) In the spectroscopy area, we did many experiments using commercially available contrast agents Gd-DTPA (an ionic contrast agent) and ProHance (a non-ionic contrast agent) to find out their influence on the in vivo brain proton spectra. We designed appropriate pulse sequences and measured their relaxivities on protons in brain metabolites (Lactate, NAA, Creatine, Choline, Myo-Inositol). The results shown that

a. after contrast injection, the metabolites spectra will change compared to that without contrast agent,

b. the change is not uniform for all brain metabolites, i.e., the relaxivities of contrast agent to protons in different molecules are different, even in the same molecule, different protons will experience different relaxation, and

c. spectroscopic quantitation after contrast agent injection can still be possible, but correction factors have to be used to calibrate the errors using the experimental results.

Computer programs in IDL (a spectrum and imaging application software) have been written to simulate the relaxation curves of these contrast agents to metabolite molecules. These results can be applied to any spectroscopic quantitation such as diseased brain and breast cancer.

6.) Photon Diffusion Imaging holds great promise as a new modality in the early detection of breast cancer. It is non-invasive, without the hazards of x-rays, and potentially much cheaper and more portable than magnetic resonance imaging. But for Photon Diffusion Imaging to be clinically useful, a number of issues must first be resolved. These involve refinement of the technique via theoretical/numerical modeling and empirical studies, and evaluation of its clinical relevance in terms of cost, effectiveness, and reliability.

Our group's path integral approach to solving the diffusion problem of photons migrating in a heterogeneous, highly scattering media has yielded substantial improvements over ballistic and search techniques. It has been used successfully to reconstruct images of phantoms and biological specimens. Current efforts are focused upon reducing the time required to generate images,

improving spatial resolution, and treating systems with more complex boundary conditions (as might be encountered in the breast).

Empirical studies have been conducted in the Hospital of the University of Pennsylvania's Radiology Department and in the University's Regional Laser and Biotechnology Laboratories. To date most of these studies have involved imaging phantoms of various geometries and optical properties while submersed in optically scattering solutions. As such they provide a test-bed for image reconstruction algorithm development and evaluation.

The following is a list of first year trainees supported this year. Also included is the period of appointment and the trainees basic scientist and clinical advisors :

Trainees	**Period of Appt.**	**Advisors**
Jeff Souris	9/1/94 - 8/31/95	Britton Chance, Ph.D. Mitchell Schnall, MD/PhD
Donald Li	8/1/94 - 7/31/95	Robert Lenkinski, PhD Barbara Fowble, MD
Enn-Ling Chen	9/1/94 - 8/31/95	John S. Leigh, Ph.D. Gilles McKenna, MD/Ph.D.
Erik Insko	6/1/95 - 5/31/96	John S. Leigh, Ph.D. Susan Orel, MD

CONCLUSIONS:

The "Predoctoral Training in Breast Cancer Detection and Treatment" has completed its highly successful first year. Four highly qualified and exceptionally well motivated trainees have been appointed in the first year. Each trainee is functioning with a dual (basic science/clinician) mentorship, which has proven to be remarkably effective.

During 1995-96 the training faculty will sponsor a special seminar series focused on breast cancer etiology, detection, and treatment. This special series will be in collaboration with the Cancer Center off the University of Pennsylvania Medical Center and the Department of Medicine and Genetics. In addition, we are in the process of adding Professor Barbara L. Weber of the Departments of Medicine and Genetics to the trainors available. Professor Weber is well known as the discoverer of the BRCA1 breast cancer gene.

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